
Distinct Metabolic States Can Support Self-Renewal and Lipogenesis in Human Pluripotent Stem Cells under Different Culture Conditions.

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Public Summary:

This study explored the impact of different growth medium on the metabolism of human pluripotent stem cells (hPSCs). While these liquid media have been validated for undifferentiated growth of hPSCs, their metabolic impact has not been explored in detail. Using advanced methods of tracking how different nutrients are used by cells, we discovered that these media induce drastic changes in the metabolic state of hPSCs. We observed a major difference in metabolism associated with lipids or fat due to a lack of lipids present in some of the newer, more chemically defined media. Some of these pathways are associated with oxidative stress responses. Supplementation of fat into these media reduced the metabolic activity and increased mitochondrial activity, providing a means for improving the metabolic state of hPSCs and their derivatives.

Scientific Abstract:

Recent studies have suggested that human pluripotent stem cells (hPSCs) depend primarily on glycolysis and only increase oxidative metabolism during differentiation. Here, we demonstrate that both glycolytic and oxidative metabolism can support hPSC growth and that the metabolic phenotype of hPSCs is largely driven by nutrient availability. We comprehensively characterized hPSC metabolism by using $(^{13}\text{C})/(^2\text{H})$ stable isotope tracing and flux analysis to define the metabolic pathways supporting hPSC bioenergetics and biosynthesis. Although glycolytic flux consistently supported hPSC growth, chemically defined media strongly influenced the state of mitochondrial respiration and fatty acid metabolism. Lipid deficiency dramatically reprogrammed pathways associated with fatty acid biosynthesis and NADPH regeneration, altering the mitochondrial function of cells and driving flux through the oxidative pentose phosphate pathway. Lipid supplementation mitigates this metabolic reprogramming and increases oxidative metabolism. These results demonstrate that self-renewing hPSCs can present distinct metabolic states and highlight the importance of medium nutrients on mitochondrial function and development.

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